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Research Article

**ROLES OF EZETIMIBE IN LIPID LOWERING AND
PREVENTING CARDIOVASCULAR DISEASES**

Abrar Saleh Alshehri

Department of Pharmacy, Khamis Mushayt General hospital,
Aseer Region, kingdom of Saudi Arabia, Khamis Mushayt,62431.

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Abstract:

One of the biggest risk factors for the development of cardiovascular disease is hypercholesterolemia. Several major cardiovascular disorders are caused by atherosclerosis caused by hypercholesterolemia. Statins are widely regarded as the preferred medication for decreasing low-density lipoprotein (LDL) cholesterol, which minimizes the morbidity and mortality associated with coronary heart disease. Because statin treatment can cause muscle issues and other side effects, non-adherence and termination of statin therapy frequently results in poor control of plasma cholesterol levels and increased cardiovascular risk. The literature was reviewed and searched through databases such as PubMed and Embase, for all relevant articles that were published till the middle of 2022. Nevertheless, there is persuasive evidence that statin-treated patients still have significant residual cardiovascular risk. When taken with statin therapy, ezetimibe increases cholesterol-lowering efficacy and provides slight extra cardiovascular protection. Although having a better safety profile than statins, ezetimibe-induced cholesterol reduction is moderate when administered alone. As a result, there is an urgent need to identify alternative effective hypolipidemic medicines that can be administered in conjunction with statins or on their own if statins are not tolerated.

Corresponding author:

Abrar Saleh Alshehri,

Department of Pharmacy, Khamis Mushayt General hospital,
Aseer Region, kingdom of Saudi Arabia, Khamis Mushayt,62431.

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INTRODUCTION:

Cardiovascular disease (CVD) refers to a group of heart and blood vessel disorders that includes coronary heart disease (heart attacks), cerebrovascular disease (stroke), hypertensive heart disease, heart failure, peripheral artery disease, rheumatic heart disease, congenital heart disease, and others [1]. CVD continues to be the largest cause of death worldwide, as well as a major cause of morbidity and disability [2]. High levels of blood cholesterol (hypercholesterolemia) are thought to be one of the major modifiable risk factors for CVD; thus, lowering cholesterol, particularly low-density lipoprotein cholesterol (LDLC), is considered an important target of therapy in the primary and secondary prevention of CVD [3,4].

Endogenous production, intestinal absorption, biliary secretion, and fecal excretion are all activities that govern cholesterol homeostasis [5]. Endogenous cholesterol production occurs in the liver and requires significant energy input, whereas exogenous cholesterol reaches the intestinal lumen mostly through dietary intake. As dietary cholesterol is absorbed from the gut lumen, lipoproteins are formed and transported to numerous tissues for energy utilization, lipid deposition, steroid hormone synthesis, and bile acid generation [6]. Biliary secretion is the primary mechanism through which the body removes cholesterol, either as an intact molecule or after breakdown to bile acids prior to fecal expulsion. Abnormalities in any of these lipoprotein metabolism processes are major risk factors for atherosclerosis [7], and elevated concentrations of one specific lipoprotein (low-density cholesterol, LDL-C) in the plasma can induce the development of atherosclerosis even in the absence of other risk factors [8].

Ezetimibe is a selective cholesterol absorption inhibitor that inhibits the intestinal absorption of dietary and biliary cholesterol, as well as related plant sterols, without altering fat-soluble vitamin, triglyceride, or bile acid intake [9]. It binds to the NiemannPick C1 Like 1 (NPC1L1) protein and inhibits enterocyte uptake and absorption of cholesterol and plant sterols via binding to the brush border of the small intestine [9]. As a result, it can reduce the supply of intestinal cholesterol to the liver, resulting in a decrease in hepatic cholesterol storage and an increase in cholesterol clearance from the blood [9].

Aim of the narrative review is to emphasize the roles of ezetimibe in preventing cardiovascular diseases by lowering the serum lipid.

METHODOLOGY:

Narrative review performed through searching the literature using medical databases PubMed and Embase, for all relevant articles that was published to the middle of 2022, using following terms; ezetimibe, cardiovascular disease, prevention. Lipid lowering agents. References of included studies were searched for more relevant studies to be useful in our review. Restrictions to only published studies in English language with human subject.

DISCUSSION:

Ezetimibe is the first and only specific inhibitor of intestinal cholesterol absorption. It is a non-statin lipid modifying medication. It is an efficient LDL cholesterol reducing medication that is both safe and well tolerated. A conventional dose of ezetimibe of 10 mg per day reduces LDL cholesterol by 13% to 20%, nonhigh density lipoprotein cholesterol (nonHDL-C) by 14% to 19%, triglyceride (TG) by 5% to 11%, and improves HDL cholesterol by 3% to 5% [10]. Ezetimibe in combination with other lipid modifying medications can result in better lipid results while having no side effects. Additionally, it has no effect on the activity of CYP450, a significant drug metabolizing enzyme, hence avoiding any potential pharmacokinetic interactions with the majority of drugs [11].

High plasma concentrations of one specific lipoprotein (low-density cholesterol, LDL-C) can cause atherosclerosis even in the absence of other risk factors [7]. Statins have been the cornerstone of therapy for lowering LDL-C to reduce the risk of both primary and secondary cardiovascular events, reducing the incidence of coronary heart disease by roughly 30% [7]. Previous statin therapy trials, most notably the Cholesterol Treatment Trialists' Collaborators (CTT) trial, suggest that the absolute reduction in LDL is primarily responsible for the proportional reduction in cardiovascular risk, and that more intensive LDL reduction results in further risk reduction [8]. The most recent ACC/AHA guidelines on the treatment of high blood cholesterol from 2013 update traditional LDL-C goals and declare that actual targets are not required. Instead, high-risk patients should strive for a 50% or greater reduction in LDL-C for significant cardiovascular risk reduction [12].

Ezetimibe is a cholesterol absorption inhibitor that acts by blocking the Niemann-Pick C1-Like 1 (NPC1L1) receptor, which is expressed at the brush border membrane of small intestine and hepatocytes. Unesterified cholesterol is integrated into mixed micelles in the small intestine lumen, which also contain bile acids, phospholipids, and triglyceride hydrolytic products. This is necessary so that cholesterol can diffuse across the unstirred water layer before being absorbed at the brush boundary membrane [13]. It was originally considered that cholesterol moved passively over the brush boundary membrane, however it is now clear that NPC1L1 mediates cholesterol transport into the enterocyte. Carriers of an NPC1L1 gene mutation have been demonstrated to have lower LDL-C levels and thus a lower risk of coronary atherosclerotic vascular disease. In addition, genetic inactivation of NPC1L1 in mice results in a reduction in intestinal cholesterol absorption similar to that found in ezetimibe-treated mice [14,15].

Aside from decreasing cholesterol absorption in the intestine, ezetimibe increases the expression of LDL receptors in the liver, lowering LDL-C levels in the bloodstream. Because the mechanism is independent and additional to that of a statin, it has been a focus of lipid-lowering therapy. A recent research of ezetimibe and statin medication on atherosclerotic disease events and all-cause mortality at a large health maintenance organization in southeastern Michigan examined their independent relationships. In this observational study, both ezetimibe (OR 0.33, 95% CI 0.13-0.86, $p=0.024$) and statins (OR 0.61, 95% CI 0.36-1.04, $p=0.068$) were associated with significantly lower odds of the primary composite endpoint of atherosclerotic disease events or all-cause mortality, with no discernible difference between the two types of lipid-lowering medication [16]. Later research looked into the interaction between statins and ezetimibe's synergistic effects. Interestingly, when used in conjunction with statin therapy, ezetimibe has been shown to lower LDL-C by an extra 23.4% compared to statin monotherapy, and the combined impact of ezetimibe and statins reduced high-sensitivity C-reactive protein (CRP) [17]. When combined with simvastatin 20 mg or atorvastatin 10 mg, ezetimibe results in a 50% reduction in LDL-C and an additional 5% reduction in LDL with each doubling of the statin dose [18,19]. Also, coadministration of 10 mg ezetimibe with each statin dose results in a higher LDL-C reduction when compared.

In certain comorbid diseases, ezetimibe has also been demonstrated to be beneficial with no increased risk. Ezetimibe has been demonstrated to minimize the first clinical cardiovascular event in patients with aortic stenosis and no established coronary artery disease [19]. In patients with known mild renal disease, it also reduces a primary composite outcome of first major atherosclerosis events. The SHARP study found that adding ezetimibe to a statin resulted in an average LDL-C decrease of 15.3 mg/dL over around 5 years, with an accompanying reduction in the risk of major atherosclerotic events (RR 0.83, 95% CI 0.74-0.94, $p=0.0021$) in patients with chronic kidney disease [19]. A significant decrease in coronary revascularization procedures was also seen, demonstrating a real-time effect on the lowering of coronary disease (RR 0.73, 95% CI 0.59-0.90, $p=0.0027$). Despite the fact that the reduction in non-fatal myocardial infarction or coronary mortality was not statistically significant (RR 0.92, 95% CI 0.76-1.11), the trial lacked the power to examine the individual components of severe atherosclerotic events [21]. Finally, ezetimibe has been found to have a minor effect on decreasing plasma fasting triglycerides as well as cholesterol in fasting and postprandial triglyceride-rich proteins in hypertriglyceridemia patients [22,23].

According to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, there is no evidence to support the routine use of non-statin medicines in conjunction with statin therapy for the reduction of incremental atherosclerotic cardiovascular disease (ASCVD) risk [12]. The guideline recommends that doctors explore adding a non-statin cholesterol lowering medicine for persons at high risk of ASCVD who have not responded adequately to statin therapy or who are intolerant to the recommended statin intensity. Similarly, the National Lipid Association (NLA) recommends non-statin drugs alone or in combination with another cholesterol lowering treatment for those who cannot tolerate a statin [10,20]. Non-statin treatments are not routinely used as monotherapy to decrease LDL-C concentrations, according to the guidelines above and other current guidelines on the management of dyslipidemia or the prevention of CVD, unless people with CVD are intolerant to statins, and they are recommended as combination therapy with statins in high-risk patients when their treatment goals are not met with the maximal tolerated dose of a statin. Ezetimibe, a non-statin medication with a unique mode of action, can be taken with a statin to provide supplementary cholesterol reduction. Combination therapy allows for a more efficient

lowering of LDL cholesterol levels than statin monotherapy. Furthermore, clinical investigations have shown that ezetimibe has a favorable safety profile with no serious side effects. However, it is unclear whether ezetimibe can lower the frequency of cardiovascular events. Furthermore, it is unknown whether its combination with other lipid modifying drugs can reduce the rate of cardiovascular events even more than other lipid modifying agent's monotherapy [19,23].

CONCLUSION:

Lipid control is one of the most effective CVD prevention techniques. Statin therapy is presently the cornerstone of treatment for decreasing LDLC in the vast majority of those at high risk of CVD. More extensive LDL-C lowering (as opposed to less intensive LDL-C lowering) based on statin monotherapy consistently lowered clinical outcomes in persons at risk of cardiovascular disease. However, some persons, particularly those at high cardiovascular risk, are contraindicated or intolerable to statin medication. Adverse effects are more common with higher intensity statin regimens. As a result, a combination of non-statin lipid modifying medications and the lowest statin dose tolerated, or, alternatively, a combination of non-statin lipid modifying therapies, represent feasible treatments for patient's intolerant to statins. Ezetimibe was approved and widely used based on a reduction in LDL-C, a proxy for cardiovascular risk reduction. However, due to conflicting outcomes in atherosclerotic imaging studies and a lack of established CV endpoint benefit, this innovative method for decreasing LDL-C became controversial over time.

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